Thinking Differently About Indication Prioritization

Considerations for Making Better Strategic Decisions

September 19, 2022

Learning Objectives

To provide participants with recommendations for how to modify current indication prioritization best practices to improve strategic decision making.

- Participants will be introduced to an innovative, robust framework for indication prioritization that has resulted in more balanced and actionable assessments of individual indications by focusing not only on traditional metrics defining feasibility, but also post launch differentiation and value creation
- The result of this evolution in approach has been improved decision making and higher corporate valuations with less risk – cases will be discussed
- Moderators from Syneos Consulting will lead the group through the following discussions:
  - Discussing current best practices for indication prioritization and common pitfalls
  - Introducing new clinical evaluation dimensions to improve assessments of clinical feasibility
  - Introducing TPP development and testing as an integral stage in prioritizing target indications
  - Defining ways of working with R&D and RWE stakeholders to ensure appropriate assumptions relating to clinical strategies and plans are developed
  - Understanding new capabilities a company may need to build or partner to enable recommended changes
  - Introducing select cases demonstrating strategic application of the prioritization exercise

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The direction of an asset coming out of discovery is the first key business decision organizations make towards ensuring that the asset will be differentiated and value creating at launch

Diligence against the dimensions below is typically derived from an historical perspective. The weakness of this approach is that the evaluation of your asset is based upon historical perceptions and behaviors.

Initial Diligence and Prioritization	High level criteria are developed to enable quick knockout of critical mass of indication options. Misalignment with organizational objectives and strategies, strength of science are key drivers
Advanced Diligence on Top Priorities	More robust research on select criteria that ladder up to the dimensions of commercial opportunity, clinical feasibility and strategic fit. Tendency to shy away from primary research and rely upon secondary sources of data
Target Indications	Multi-attribute modeling or less complex prioritization methodologies used to force rank or segment the indication opportunities.

Upside

- ✓ *Robust*
- ✓ *Data Driven*
- ✓ *Repeatable*
- ✓ *Consistent*

Downside

- × *Too Formulaic*
- × *Historical Precedents*
- × *Analogs vs. Asset*

Markets are becoming much more complex, and they are changing rapidly. More traditional methods of assessing indication opportunities may lose sight of the asset and not capture complexities inherent in evolving markets.

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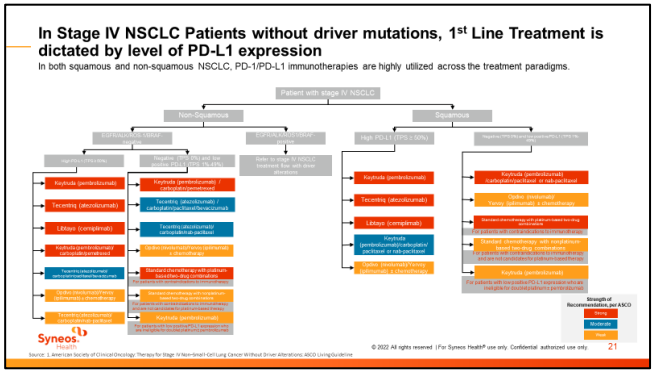
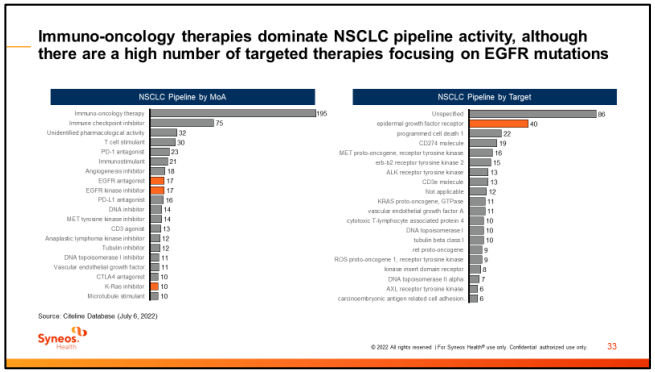
The need for changing the way we approach indication prioritization is best exemplified in oncology

A little more than 10-years ago the metastatic NSCLC market was relatively easy to navigate with just platinum-based chemotherapy and 1st generation EGFRs available ……..

Today the metastatic market looks more like a collection of rare diseases and the pace of development continues……..





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Strategic decision making can be improved by modest investments in modifications to the framework that are more specific to the asset and forward looking

At Syneos Health, we have modified our prioritization framework to include clinical and commercial criteria that are forward looking, and asset focused.

Initial Diligence and Prioritization

Advanced Diligence on Top Priorities

Target Indications and Indication Sequence

Clinical and commercial collaboration to develop:

- *Market evolution scenarios*
- *Pre-clinical requirements*
- *Early phase requirements*
- *High level operational feasibility*
- *Target product profile*
- *Aligned Phase 3 strategy*

Actualization of this model requires collaboration across multiple subject matter experts: early stage, clinical operations, medical and commercial.

However, the payoff is better decision making and organizational alignment early on around what it is going to take to develop an asset that is truly differentiated.

Our objective during the advanced diligence phase is to project different market evolution scenarios and understand how the product will need to be developed in order to be differentiated and create value at launch.

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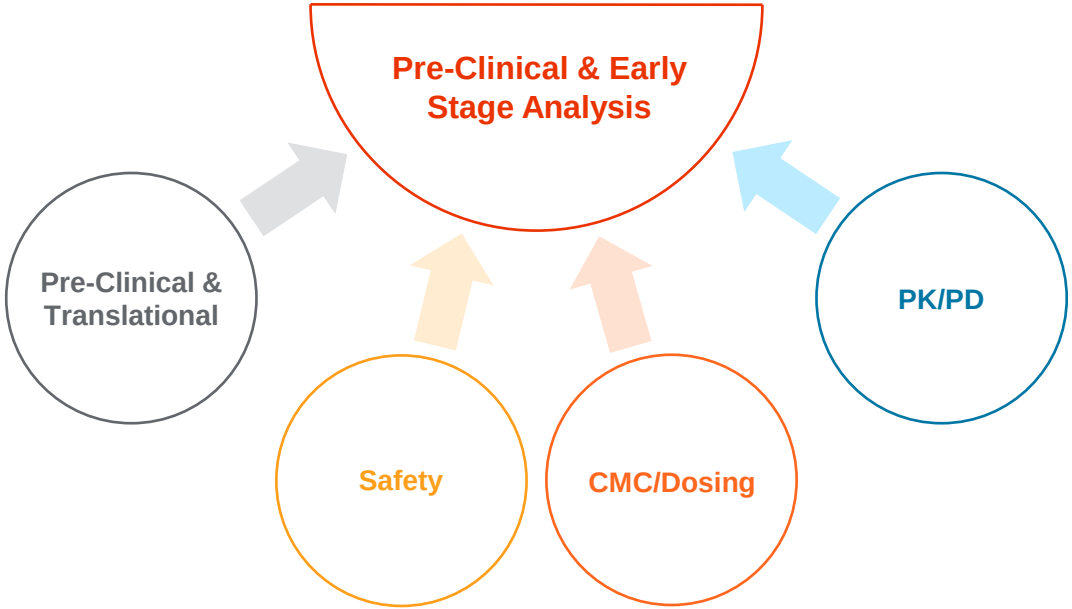
Assessing early-stage pre-clinical and clinical requirements specific to the asset provides a point of view commonly overlooked when assessing clinical feasibility

Pre-clinical and early-stage requirements are commonly overlooked and for many indications can be a significant driver of time and cost. For instance, the search for treatment naïve patients today in conditions like PNH can be very challenging.



- Drugability and bioaffinity?
- How big of a dose is needed?
- What is the extent of safety data to support duration?
- What types of models are needed?
- What is the feasibility of recruiting patients?
- Technical feasibility of hitting TPP?

Current prioritization methodologies are heavily indexed to the link between the MOA/indication and pathways. Deeper asset specific early-stage diligence can provide a completely different picture of the opportunity.

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Adding TPP development and testing to the prioritization framework ensures that we remain focused on the asset and value creation

At Syneos Health, the initial profile is developed collaboratively between clinical, medical and commercial subject matter experts. It is then validated and refined by primary market research with KOLs. The key is selecting the right KOLs!

Key Syneos SMEs collaborate to…

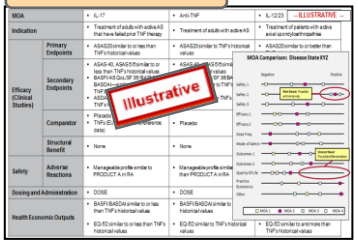
- Clinical/Regulatory
- \+
- Medical
- \+
- Consulting

…. assess future landscape and strategic positioning driving success,

- ✓ How will the market evolve?
- ✓ What will be new SOC?
- ✓ What will be the target patient population?
- ✓ Type of endpoints we will need to assess?
- ✓ Expected magnitude of endpoints?

…. and develop an initial TPP that is validated and refined through PMR.

Initial TPP



Leverage clinical and medical SMEs to diligently select the external stakeholders to interview

The key is projecting the future environment and understanding how the asset will need to be strategically positioned for it to be differentiated and value creating at launch.

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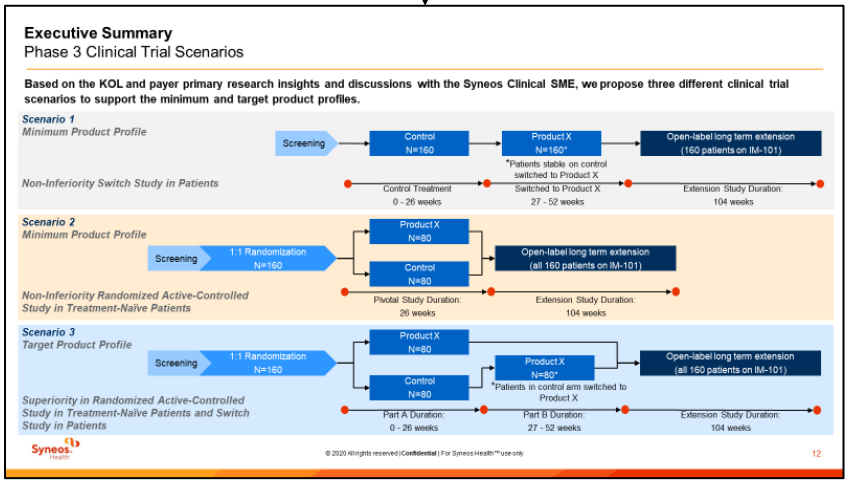
The TPP approach shifts the feasibility conversation from an examination of analogs to a real-world discussion of the clinical path required to pull-through the target label

Normally, we would use benchmarks to assess the clinical path, estimate trials designs, length, etc. Although sound methodologically, the approach can lead to spurious conclusions, especially in markets that are evolving rapidly.

Redacted Examples

Clinical Strategy Derived from TPP to Better Assess Feasibility

Category	Product Profile			Rationale/Assumptions
MOA	Anti-complement factor C5 monoclonal antibody			
Indication	Induction of remission in patients with active GPA or MPA			▪ Assumed an induction trial similar to rituximab ▪ Potentially faster study results (1 year of therapy with IM-101), but recruitment may be challenging as patients need to be identified and treated during an active inflammation episode
Pivotal Trial Design	Randomized, double-blind, active controlled (cyclophosphamide), N=200			Benchmarked to rituximab induction trial
Study Population	▪ Adult subjects with GPA or MPA and positive test for anti-PR3 and anti-MPO antibodies ▪ Newly diagnosed or relapsed patients ▪ Active and severe disease ▪ Patients to be vaccinated for meningococcal infections prior to study			▪ Typical study design for GPA/MPA induction trials ▪ Focus on GPA or MPA, primarily because of strength of biological hypothesis of C5 complement in these particular disease subtypes
ROA and Dosing	▪ IV infusion once weekly for 4 weeks			▪ Confirmed by ImmunAbs
Efficacy	**Endpoint**	**Product X**	**Active Control (Cyclophosphamide)**	**Benchmarked to rituximab induction trial** ▪ % of patients achieving CR, and off GC at 6 months = 64% (RTX) vs. 53% (CYC) [non-inferiority] ▪ % of patients achieving CR, while at <10mg/d GC dose at 6 months = 71% (RTX) vs. 62% (CYC) [non-inferiority] ▪ Rates of severe disease flares = 0.011 (RTX) vs. 0.018 (CYC)
	% of patients achieving complete remission (CR), and off GC therapy at 6 months	70% (Superiority)	53%	
	% of patients achieving CR, while at <10mg/d GC dose at 6 months	80% (Superiority)	62%	
	Rates of severe disease flares	0.005 /patient/month	0.018	
	QoL (SF36 and EQ-5D-5L): Statistically significant improvements in quality of life vs. control			
Safety	**Warnings**: Serious infections with Neisseria species, Aspergillus, Streptococcus pneumoniae and Hemophilus influenzae type B **Top AEs (vs. control):** Headaches (44% vs. 27%), nasopharyngitis (23% vs. 18%), back pain (19% vs. 9%), nausea (16% vs. 11%), fatigue (12% vs. 2%), infections (39% vs. 47%)			Benchmarked to Soliris® study vs. placebo in PNH due to lack of safety data from other complement inhibitors in AAV CYC infection rate sourced from rituximab trial
Storage Conditions	2°C - 8°C			Confirmed with ImmunAbs
Pricing	~ $80,000 per patient per year			Confirmed with ImmunAbs; Rituxan price = ~$20K/p/yr



We made this point earlier, but it's worth repeating the organizational benefit of gaining alignment early on to the type of labeling and clinical strategy required to achieve success in the marketplace.

The TPP approach then engenders an integrated (Medical, Clinical, Commercial) and more robust discussion of whether the organization is willing to make the investments and take the risks

How do we feel about Phase 3 requirements …….

Illustrative

Strategically Aligned	Aligned Capabilities	Degree of Difficulty	Tradeoffs
• Alignment to corporate objectives • Financial constraints • Timelines • Risk tolerance	• Are internal capabilities available • Is there a suitable partner • Cost and timing of capability development	• Complexity of trial • Patient population • Mix of endpoints • Magnitude of response	• Implications of minimally acceptable TPP • Risk of a miss

You'll note that the evaluation criteria really do not change. However, how we score them could change considerably from more traditional methods.

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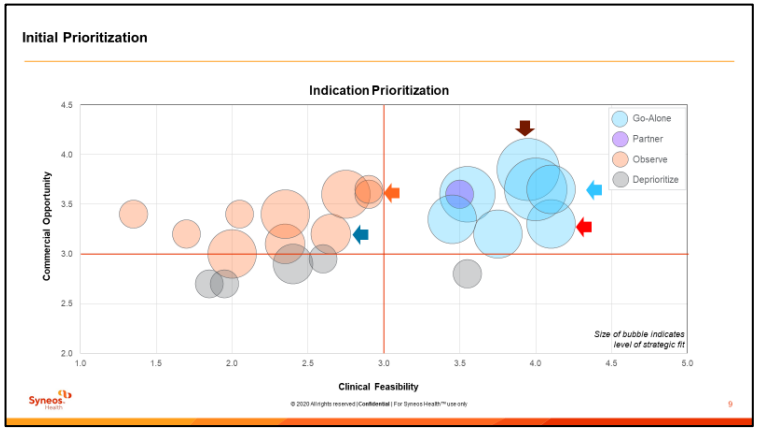
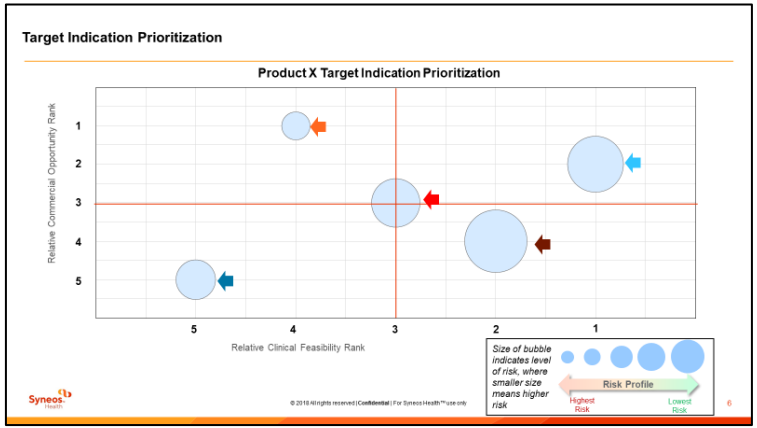
Your prioritization model can then be rerun with the asset specific data and the yield can be much different than expected

The redacted case below illustrates how the situation can change as focus shifts to include early-stage requirements and future state value creation.

This is an interesting example as the Client wanted a deep dive into all the indications, followed by closer examination of early-stage requirements and TPP.





Our modified approach should yield sufficient data to support transition right into strategy, and from there into more in-depth clinical development planning.

Implementation of the New Methodology: Degree of Difficulty

Clearly making the change requires new capabilities and process changes.

What's required?
• Philosophical change • Additional budgeting • New ways of working between NPP and R&D • Broad indication expertise • KOL identification and recruitment • Modification of the existing frameworks

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Case Study

Indication Prioritization Case Study: Overview

An emerging antibody therapeutics-specialized company was interested in assessing and prioritizing the opportunity for their discovery stage asset across multiple rare indications in the US, EU5 and Korea.

Business Problem

- Product's mechanism of action potentially enables treatment of multiple rare inflammatory diseases
- Highly variable market dynamics and clinical development across these disease areas, complicating client's ability to accurately assess the future state
- Relatively newer staff with expertise in antibody design and process development, and lacking prior clinical development and commercialization experience
- Client sought assistance in assessing the opportunity for their lead asset across multiple rare indications of interest for investment in clinical development

Actions Taken

Step 1	Screening Pillars	Syneos Capability
Initial Disease Screen of 22 indications to select 5 target indications for deeper dive analysis	Commercial Potential	Consulting
	Clinical Feasibility	Clinical
	Strategic Fit	Consulting, Clinical, Selling Solutions

Step 2	Key Components	Syneos Capability
Landscape Assessment	Market Dynamics (e.g., size, competition, access, etc.)	Consulting
	Clinical Trials Analysis (e.g., endpoints, timelines, etc.)	Clinical and Consulting

Step 3	Methodology	Syneos Capability
Winning-Label Analysis	TPP Design	Consulting and Clinical
	Test TPP with KOLs, Payers, and Clinical SMEs	
	Formulate winning label profile and clinical strategy	

Step 4	Methodology	Syneos Capability
Final Prioritization and strategy	Rank 5 indications on the basis of commercial potential, clinical feasibility, and level of risk	Consulting

Project Outcome

- Gauging organization's capabilities and preliminary product profile, Syneos Health outlined key commercial and clinical considerations for the leadership team to support selection of final priority indication(s) for further development of their lead asset and the overarching indication strategy.

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